Research Article

Augmented Glycemic Gap is a Marker for Predicting the Early Neurological Outcomes in Acute Ischemic Stroke Patients Treated with Intravenous Thrombolysis

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Abstract

Background and Purpose: Glycemic Gap (GG) as an index reflecting the acute fluctuation of glycemia, has been proved to be associated with poor functional outcomes in Acute Ischemic Stroke (AIS) patients. However, it predictive value on post-thrombolysis Early Neurological Outcomes (ENOs) are still controversial. This study aimed to use GG to evaluate the influence of pretreatment relative glucose changes on post-thrombolysis ENOs, and we further explored the predictive value of GG in different glycemic control status.

Methods: Early Neurological Deterioration (END) was defined as a National Institutes of Health Stroke Scale Score (NIHSS) ≥4, Early Neurological Improvement (ENI) was defined as a ≥4-point decrease in NIHSS score or a complete resolution of neurological deficits, between the time of admission and 24 hours after intravenous recombinant tissue-type plasminogen activator (IV-rtPA). GG was calculated as Admission Blood Glucose level (ABG)- estimated average blood glucose level (eAG), eAG could be derived from HbAlc according to the equation eAG=28.7*HbAlc-46.7

Results: Increased GG was significantly associated with post-thrombolysis END and poor functional outcome at discharge (OR, 1.982; 95% CI, 1.213-3.238; P=0.006) (OR, 2.079; 95% CI, 1.305-3.312; P=0.002). Its predictive value on END was more pronounce in diabetic patients (OR, 2.434; 95% CI, 1.079-5.491; P=0.032), after dichotomizing glycemic control status, its significance was only maintained in diabetic patients with good previous glucose control (OR, 6.946; 95% CI, 1.217-39.636; P=0.029).

Conclusion: An evaluated GG was associated with high risk of post-thrombolysis END and poor functional outcome at discharge in AIS patients, and the previous glucose control should be considered when predicting ENOs.

Keywords: Acute ischemic stroke; Early neurological deterioration; Poor functional outcome; Glycemic gap; Stress induced hyperglycemia

Introduction

Stress-Induced Hyperglycemia (SIH) is a common phenomenon during acute phase of severe illness, it could be a hallmark of diseases severity [1]. SIH controlled background glycemia reflects the fluctuation of glucose in the acute phase of the diseases. The underlying mechanisms involves activation of hypotha-lamic-pituituary-adrenal axis and sympatho-adrenal system, reflects the severity of physiological stress [2]. Glycemia Gap (GG) is a novel index of glycemic excursion to quantifies the relative glycemic rise from chronic glycemia in the acute phase of illness. Previous studies have confirmed that GG is a useful marker for predicting poor outcomes after some critical illness, including ischemic stroke [3-5]. However, the prognostic value of GG requires comprehensive consideration patients previous glucometabolic level. The deleterious effects of increased GG was more pronounce in diabetic patients [6], according to the results of one study, the effect of elevated GG on poor func-

tional outcome was more significant in diabetic patients with good previous glucose control [3].

Early Neurological Deterioration (END) after Acute Ischemic Stroke (AIS) is a prominent clinical issue that is strongly correlated with poor functional outcome and mortality [7,8]. In our previous study, we found that Stress Hyperglycemia Ratio (SHR), which is calculated as Admission Blood Glucose (ABG) level divided by glycosylated hemoglobin (HbAlc %), was significantly associated with END, and this association is more pronounced in diabetic patients [9]. Compared with SHR, the GG was calculated as ABG minus the estimating blood glucose (eAG) determined by HbAlc [10], reflecting the absolute difference from eAG [11]. The predictive value of GG on END is unclear. Therefore, the aim of this study was to validate its predictive value on Early Neurological Outcomes (ENO), and we further explored the whether the predictive effects is different in AIS patients with different previous glucose metabolism.

Method

Study Population

This study retrospectively included consecutive patients with AIS treated with intravenous recombinant tissue-type plasminogen activator (IV-rtPA) at the Department of Neurology, Center of Cerebrovascular Disorders, ChangHai Hospital and Department of Neurology, The Second Affiliated Hospital of Xu Zhou Medical School from January 2017, to December 2020. Patients enrolled in this study if they: (1) aged 18 years or older; (2) were admission within 4.5h after onset; and (3) were treatment with IV-rtPA. Patients were excluded from this study if they: (1) were diagnoses of malignant tumors, autoimmune diseases, major organ failure or presence of an active infection; and (2) had incomplete clinical data. We further excluded patients treated with IV-rtPA and endovascular thrombectomy to maintain the homogeneity of the enrolled patients. Written informed consent was obtained from participants or legal representatives. The study protocol was approved by Ethics Committee of ChangHai Hospital and The Second Affiliated Hospital of Xu Zhou Medical School.

Baseline Assessments

Stroke severity was assessed via National Institutes of Health

Table 1: Baseline Characteristics of subgroups based on the tertile of glycemic gap.

	T1 (n=266)	T2 (n=266)	T3 (n=266)	P
Demographics				
Age, mean (SD), y	67(10.9)	66(11.4)	67(11.9)	0.718
Male, n (%)	178(66.9)	171(64.3)	163(61.3)	0.398
Vascular risk factors				
Hypertension, n (%)	169(63.5)	195(73.3)	179(67.3)	0.051
Diabetes millets, n (%)	99(37.2)	52(19.5)	128(48.1)	<0.001
Atrial fibrillation, n (%)	37(13.9)	36(13.5)	37(13.9)	0.990
Coronary heart disease, n (%)	36(13.6)	28(10.6)	37(14.0)	0.437
Previous stroke, n (%)	55(20.7)	48(18.0)	52(19.5)	0.744
Current smoking, n (%)	113(42.5)	114(42.9)	92(34.6)	0.089
Current drinking, n (%)	54(20.3)	70(26.3)	63(23.7)	0.260
Clinical data				
SBP, mean (SD), mmHg	151(18.8)	156(22.3)	153(23.0)	0.019
DBP, mean (SD), mmHg	87(13.1)	89(14.8)	87(13.2)	0.182
Admission NIHSS, median (IQR)				
Previous antiplatelet, n (%)	58(21.8)	41(15.4)	50(18.8)	0.167
Proximal artery occlusion, n (%)	14(5.3)	15(5.6)	20(7.5)	0.510
OTT, mean (SD), min				
Stroke subtype, n (%)				0.041
LAA	62(23.3)	76(28.6)	98(36.8)	
CE	35(13.2)	38(14.3)	34(12.8)	
SAO	132(49.6)	114(42.9)	103(38.7)	
Others and Undetermined	37(13.9)	38(14.3)	31(11.7)	
END, n (%)	35(13.2)	38(14.3)	66(24.8)	<0.001
ENI, n (%)	83(31.2)	70(26.3)	54(20.3)	0.016
sICH, n (%)	4(1.5)	5(1.9)	6(2.3)	0.816
Poor functional outcome, n (%)	31(11.7)	44(16.5)	140(52.6)	<0.001
Laboratory data				
PLT, median (IQR)	208.0(170.0-249.0)	211.0(174.0-274.0)	203.0(166.0-251.5)	0.450
TG, median (IQR), mmol/L	1.4(0.9-1.9)	1.3(0.9-1.9)	1.3(0.9-1.8)	0.577
LDL, median (IQR), mmol/L	2.9(2.3-3.5)	3.0(2.4-3.6)	3.0(2.4-3.5)	0.315
HDL, median (IQR), mmol/L	1.2(1.0-1.4)	1.2(1.1-1.4)	1.2(1.0-1.4)	0.019
WBC, median (IQR)	7.2(5.9-8.9)	7.7(6.2-9.2)	7.6(6.2-9.2)	0.173
NLR, median (IQR)	2.3(1.6-3.6)	2.4(1.6-3.8)	2.8(1.9-4.5)	0.001

SD: Standard Deviation; IQR; Interquartile Range; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; NIHSS: National Institutes of Health Stroke Scale; OTT: Onset-To-Treatment; LAA: Large Artery Atherosclerosis; CE: Cardio Embolism; SAO: Small Artery Occlusion; END: Early Neurologcal Deterioration; ENI: Early Neurological Improvement; SICH: Symptomatic Intracranial Hemorrhage; PLT: Platelet; TG: Triglyceride; LDL: Low-density Lipoprotein; HDL: High-density Lipoprotein; WBC: White Blood Cell Counts; NLR: Neutrophil-to-Lymphocyte Ratio

Table 2: Clinical outcomes of subgroups based on the presence diabetes mellitus.

	Non-diabetic				Diabetic			
	T1 (n=173)	T2 (n=173)	T3 (n=173)	P	T1 (n=93)	T2 (n=93)	T3 (n=93)	P
Clinical outcomes								
END, n (%)	21(12.1)	21(12.1)	38(22.0)	0.014	12(12.9)	20(21.5)	27(29.0)	0.026
ENI, n (%)	48(27.7)	45(26.0)	44(25.4)	0.879	29(31.2)	27(29.0)	14(15.1)	0.022
Poor outcome, n (%)	33(19.1)	35(20.2)	60(34.7)	0.001	21(22.6)	28(30.1)	38(40.1)	0.026

END: Early Neurological Deterioration; ENI: Early Neurological Improvement; P for trend

Table 3: Multivariate logistical regression analyses depicting the association of GG and respective outcomes.

outcomes	GG	OR	95% CI	P
END	T1	Ref		
	T2	1.034	0.604-1.768	0.904
	T3	1.982	1.213-3.238	0.006
ENI	T1	Ref		
	T2	0.761	0.512-1.129	0.175
	T3	0.492	0.322-0.752	0.010
Poor outcome	T1	Ref		
	T2	0.981	0.594-1.618	0.939
	T3	2.079	1.305-3.312	0.002

END: Early Neurological Deterioration; ENI: Early Neurological Improvement; GG: Glycemic Gap; OR: Odd Ratio; CI: Confident Interval; P for trend.

Stroke Scale (NIHSS). The Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria was used to classified stroke subtype [12]. The diagnosis of Symptomatic Intracranial Hemorrhage (sICH) was based on the results of CT scans, combined with a NIHSS score of ≥4. A poor functional outcome at discharge was defined as a Modified Rankin Scale (mRS) score of 3-6 at discharge. The mRS score were collected the day before discharge by two trained physicians independent of the study. The proximal artery occlusion confirmed by the Computed Tomography Angiography (CTA), Magnetic Resonance Angiography (MRA) and Digital Subtraction Angiography (DSA). Image data were reviewed in blind manner by two physicians, with advice of the third experienced physicians in case of disagreement.

Definition of Post-Thrombolysis Early Neurological Outcome

The post-thrombolysis END was defined as a ≥4-point increase in NIHSS score between the time of admission and 24 hours after IV-rtPA [13]. Meanwhile post-thrombolysis ENI was defined as a ≥4-point decrease in NIHSS score or a complete resolution of neurological deficits between the time of admission and 24 hours after IV-rtPA [14,15]. Neurological deficit was evaluated on admission and at 24 hours after IV-rtPA by two certified neurologists blinded to the clinical data.

Assessment of Glycemic Gap

Fasting plasm glucose levels were monitored shortly after admission before IV-rtPA. Glycosylated hemoglobin (HbAlc%) was measured within 24 hours after hospitalization, estimated average blood glucose level (eAG) could be derived from HbAlc according to the equation $eAG=28.7*HbAlc-46.7$ [10]. GG was calculated as ABG-eAG [11].

Assessment of Abnormal Glucose Metabolism Status

According to the recommended of American Diabetes Association (ADA), DM was diagnosed based on prior history of diabetes or an HbAlc ≥6.5% and patients with HbAlc less than 5.7% were classified as NGM [16]. Diabetic patients were classified into 2 groups according to PGC, diabetic patients with good

PGC had HbAlc <7%, diabetic patients with poor PGC had HbAlc ≥7% [16]. Patients HbAlc was measured within 24 hours after hospitalization. Admission blood glucose was measured shortly after arrived the emergency room, hyperglycemia was defined as blood glucose levels higher than 7.8mmol/L [17].

Statistical Analysis

The Kolmogorov–Smirnov test was performed to test the normality of variables, and continuous variables were described as the mean (standard deviation) and median (quartile) based on the normality of the data. Categorical variables are expressed as percentages. Differences in the baseline characteristics were assessed by χ^2 test for categorical variables and ANOVA or Kruskal–Wallis test for continuous variables.

Multivariate logistical regression was performed to analysis the association of GG and early neurological outcome, patients were tertiled according to the GG value, the first tertile group as the reference category. The covariates entered in the multivariable logistical regression were age, gender admission NIHSS, Neutrophil to Lymphocyte Ratio (NLR), time of Onset To Treatment (OTT), proximal artery occlusion, stroke subtype, sICH. The Receiver Operating Characteristic (ROC) curve was used to determine the accuracy of GG in predicting ENOs in AIS patients treated with IV-rtPA, two-tailed P values of <0.05 were considered statistically significant. Data analyses were performed using the statistical software package SPSS 22.0 for Windows (IBM, Armonk, NY).

Results

Baseline Characteristics

A total of 798 AIS patients treated with IV-rtPA were included in this study, 139(17.4%) patients had END, 207(25.9%) patients had ENI and 215(26.9%) patients had poor function outcome. Patients were tertiled according to the GG value, the baseline characteristics were presented in table 1. Patients in the higher GG group were more likely to have higher systolic blood pressure (151 vs. 156 vs.153; P=0.019); to have a higher incidence of large artery atherosclerosis and DM (23.3% vs. 28.6% vs. 36.8%; P=0.041) (37.2% vs. 19.5% vs. 48.1%; P<0.001); to have a higher occurrence of END and poor functional outcome at discharge (13.2% vs. 14.3% vs. 24.8%; P<0.001) (11.7% vs. 16.5% vs. 52.6%; P<0.001); to have a higher level of NLR (2.3 vs. 2.4 vs. 2.8; P<0.001). Patients were less likely to experience post-thrombolysis ENI in the higher GG tertile group (31.2% vs. 26.3% vs. 20.3%; P=0.016).

In table 2, Patients were divided into non-diabetic and diabetic groups, in both groups patients in the higher GG group have a higher risk of END and poor functional outcome at discharge (12.1% vs. 12.1% vs. 22.0%; P=0.014) (12.9% vs. 21.5% vs. 29.0%; P=0.026) (19.1% vs. 20.2% vs. 34.7%; P=0.001) (22.6% vs. 30.1% vs. 40.1%; P=0.026). In the diabetic group, patients more likely to experienced ENI in the lower GG group (31.2% vs. 29.0% vs. 15.1%; P=0.026).

Table 4: Multivariate logistical regression analyses depicting the association of GG and respective early neurological outcomes in patients with and without DM.

Outcome	GG	Non-diabetic			Diabetic		
		OR	95% CI	P	OR	95% CI	P
END	T1	Ref	Ref		Ref	Ref	
	T2	1.053	0.548-2.025	0.877	1.790	0.768-4.172	0.177
	T2	1.657	0.843-3.258	0.143	2.434	1.079-5.491	0.032
ENI	T1	Ref	Ref		Ref	Ref	
	T2	0.777	0.468-1.291	0.330	0.878	0.452-1.703	0.700
	T3	0.835	0.471-1.480	0.537	0.374	0.173-0.806	0.012
Poor outcome	T1	Ref	Ref		Ref	Ref	
	T2	1.224	0.657-2.281	0.532	1.410	0.628-3.163	0.405
	T3	2.536	1.337-4.812	0.004	2.423	1.099-5.344	0.028

END: Early Neurological Deterioration; ENI: Early Neurological Improvement; CI: Confident Interval; OR: Odds Ratio; SHR: Stress Hyperglycemia Ratio; P for trend.

Table 5: Multivariate logistical regression analyses depicting the association of GG and respective early neurological outcomes in DM patients with different previous glucose ccontrol.

DM	GG	Good-PGC			Poor-PGC		
		OR	95%CI	P	OR	95% CI	P
END	T1	Ref	Ref		Ref	Ref	
	T2	2.690	0.417-17.346	0.298	1.542	0.620-3.839	0.352
	T2	6.946	1.217-39.636	0.029	1.511	0.617-3.705	0.367
ENI	T1	Ref	Ref		Ref	Ref	
	T2	0.672	0.225-2.003	0.475	1.266	0.534-2.998	0.592
	T3	0.283	0.081-0.993	0.049	0.182	0.051-0.646	0.008

DM: Diabetes Mellitus; END: Early Neurological Deterioration; ENI: Early Neurological Inprovement; GG: Glycemic Gap; PGC: Previous Glucose Control; OR: Odd Ratio; CI: Confident Interval; P for trend.

Association of GG and Early Neurological Outcomes in Multivariate Analysis

Multivariate logistical regression was performed to analyze the relationship between GG and early neurological outcomes for all patients and for the subgroups of patients with different states of glucose metabolism. The results are showed in table 3,4 and 5. After adjusting for confounders, the risk of END and poor functional outcome at discharge was significantly higher in third tertile group than those of patient in the first tertile group (as the reference value) (OR, 1.982; 95% CI, 1.213-3.238; P=0.006) (OR, 2.079; 95% CI, 1.305-3.312; P=0.002). However, the probability of ENI is significantly lower in the third tertile group (OR, 0.492; 95% CI, 0.322-0.752; P=0.010). In the subgroups analysis, the predictive effect of increased GG on END and ENI was significant only for diabetic patients (OR, 2.434; 95% CI, 1.079-5.491; P=0.032) (OR, 0.374; 95% CI, 0.173-0.806; P=0.012). However, augmented GG was significantly associated with poor functional outcome at discharge in both the non-diabetic and diabetic groups (OR, 2.536; 95% CI, 1.337-4.812; P=0.004) (OR, 2.423; 95% CI, 1.099-5.344; P=0.028). Table 5 illustrated that predictive value of increased GG on END was more pronounce in diabetic patients with good previous glucose control (good-PGC) (OR, 6.946; 95% CI, 1.217-39.636; P=0.029), however, its effect on ENI was significant both in diabetic patients with poor previous blood glucose control (poor-PGC) and good-PGC (OR, 0.182; 95% CI, 0.051-0.646; P=0.008) (OR, 0.283; 95% CI, 0.081-0.993; P=0.049).
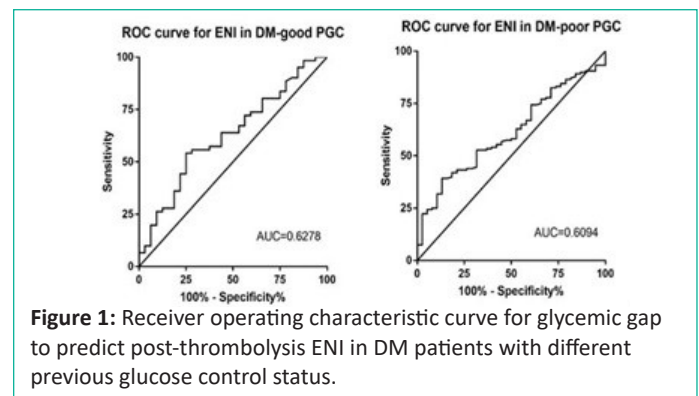

Figure 1: Receiver operating characteristic curve for glycemic gap to predict post-thrombolysis ENI in DM patients with different previous glucose control status.
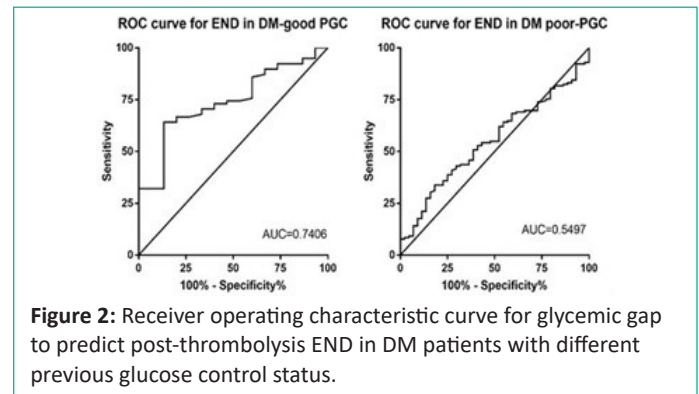

Figure 2: Receiver operating characteristic curve for glycemic gap to predict post-thrombolysis END in DM patients with different previous glucose control status.

ROC Curves were used to Test the Overall Discriminative Ability of GG for Early Neurological Outcomes in DM with Different PGC Status

ROC curves were presented in Figure1, 2. We founded that the Area Under Curve (AUC) of GG to discriminate post-thrombolysis Early Neurological outcomes (END and ENI) in DM patients with good-PGC and poor-PGC were 0.741 (95% CI, 0.621-0.862), 0.550 (95% CI, 0.460-0.640), 0.628 (95% CI, 0.510-0.746), 0.609 (95% CI, 0.519-0.699). The optimal cutoff values of GG on post-thrombolysis END and ENI in DM with different PGC was established based on the highest Youden index, the results were described in additional file1: table S1.

Discussion

This study indicated that the augment GG has adverse effect on early neurological outcomes in AIS patients treated with IV-rtPA. Moreover, we found that the deleterious effect of increased GG differ among different glucose metabolism status, the predictive effect on early neurological outcomes was more pronounced in diabetic patients, and after dichotomizing PGC status, its significance for post-thrombolysis END was only maintained in DM with good-PGC group.

According to this study, we confirmed the adverse effects of increased GG, and compared with our previous study, we used ABG level divided by glycosylated hemoglobin (HbAlc %) to represent stress-induced hyperglycemia [9], the value of GG can better reflect absolute changes of glycemia by controlling for background glycemia. Previous studies have demonstrated that GG was significantly associated with worse outcome in critically ill patients with DM [18]. In patients with acute ischemic stroke, GG might be useful in assessing disease severity and prognosis [11]. The underlying mechanisms between increased GG and END is unclear, possible explanations are acute stress response involves activation of the hypothalamic-pituitary axis and sympatho-adrenal system and promote the releases of epinephrine, norepinephrine and pro-inflammatory cytokines (TNF-α, IL-1 and IL-6) [2]. The greater inflammatory and neurohormonal mediates the breakdown of Blood-Brain Barrier (BBB),

increased the risk of brain edema and hemorrhage after reperfusion [19]. Pro-inflammatory environment and hyperglycemia may facilitate the glucose uptake in center nervous system, cellular glucose overload increases brain lactate production and further promotes the conversion of asymptomatic tissue to symptomatic tissue [20]. In addition, the increased GG reflects greater glycemic variability in AIS patients treated with IV-rtPA, previous study have shown the greater glycemic variability in AIS patients may be correlated with lower odds of ENI during hospitalization [21]. The specific triggering effect of glucose fluctuation on oxidative stress is likely to be the culprit [22].

In this study, we found the AIS patients with diabetes were more prone to experienced post- thrombolysis END, especially in those with good previous glucose control. This conclusion is consistent with previous studies reporting that admission GG was associated with poor stroke prognosis, and its predictive effect seems more significant in DM with good-PGC [3,11]. The exact pathomechanism is undetermined, possible explanations are that chronic hyperglycemia was associated with vascular remodeling and influence collateral circulation [23], AIS patients with diabetic microangiopathy were more sensitivity to ischemia and hypoxia, the over consumption of intracellular oxygen results in deepening and an extension of hypoperfusion. In addition, hyperglycemia and hyperinsulinemia can decrease the fibrinolytic activity by increasing the production of plasminogen activator inhibitor, further affects the activity of rt-PA and impaired recanalization after AIS [24]. In diabetic patients, the risk of vascular complications and death were strongly associated with previous glycemic exposure [25], the glucose fluctuation may be more common phenomenon in poor-PGC group, therefore, when suffering an acute stress, the tolerance mechanisms may be established to some extent in those patients, oxidative stress and inflammatory response may be relatively mild than DM with good-PGC. Moreover, diabetic patients with poor-PGC have a higher baseline glucose level, the threshold GG value of affecting prognosis might be more higher than good-PGC group.

The present study has several potential limitations that should be addressed when interpreting the results. First, this is a retrospective study; approximately one-fifth of the patients were excluded because they lacked HbAlc values, and we excluded patients treated with endovascular therapy after IV-rtPA, which inevitably produced biases. Second this study did not complete pre-stroke medication information, especially the use of hypoglycemic drug. Third, this study was performed in a single country, which might limit the generalizability of the results to other patient cohorts. However, the strengths of this study include the large sample size and the fact that patients were selected from multiple centers via strict inclusion and exclusion criteria.

Conclusion

In conclusion, the augment GG have a predictive value on post-thrombolysis ENO, and the previous glycemia control status will influence the predictive value of GG. This conclusion suggests that GG might become an important modifiable therapeutic target in prevention of post-thrombolysis ENO and poor functional outcome.

Author Statements

Statement of Ethics

This study was conducted according to the protocol approved by the Human Subjects Research Ethics Committee of ChangHai Hospital and The Second Affiliated Hospital of Xu Zhou Medical School.

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